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NIDN-10394

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	O. Homestad	Group Art Unit:	To be assigned
Serial Number:	09/923,074	Examiner:	To be assigned
Filing Date:	August 6, 2001		
Title:	Preparation of Iodixanol		

COMPLETION OF CLAIM FOR PRIORITY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby submit the official certified copy of the priority document number **GB 9903109.8** in connection with the above identified application, benefit of which is claimed in the declaration of this application. The Examiner is most respectfully requested to acknowledge receipt of this certified copy in the next Official Office Action.

Respectfully submitted,

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Attorney for Applicants

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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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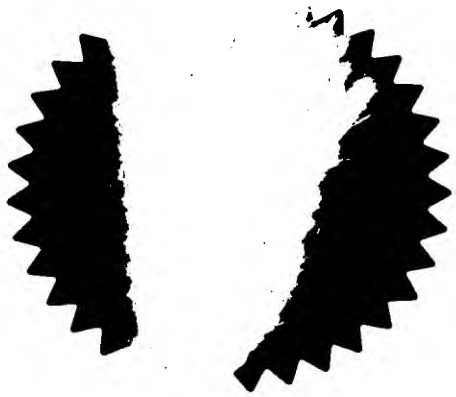

Signed P. Mahoney

Dated 21 August 2001

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1/77

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(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. **Your reference** 33.69198

2. **Patent application number** *(The Patent Office will fill in this part)* **9903109.8**

3. **Full name, address and postcode of the or of each applicant** *(underline all surnames)*

Nycomed Imaging AS
Nycoveien 1-2
N-0401 Oslo
NORWAY

Patents ADP number *(if you know it)* 6246961001

If the applicant is a corporate body, give country/state of incorporation Norway

20/8/91

4. **Title of the invention** Process

Form 5/77

5. **Name of your agent** *(if you have one)* Frank B. Dehn & Co.

A S Rollins et al
Amersham plc
Amersham Laboratories
White Lion Road
Amersham
HP7 9LL

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
179 Queen Victoria Street
London
EC4V 4EL

Patents ADP number *(if you know it)* 166001

6. **If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and** *(if you know it)* **the or each application number**

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. **If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application**

Number of earlier application	Date of filing *(day / month / year)*

8. **Is a statement of inventorship and of right to grant of a patent required in support of this request?** *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or Yes
b) there is an inventor who is not named as an applicant, or
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Patents Form 1/77

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Continuation sheets of this form	
Description	7
Claim(s)	2
Abstract	1
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature  Date 11 February 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

H.J. Skailes
0171 206 0600

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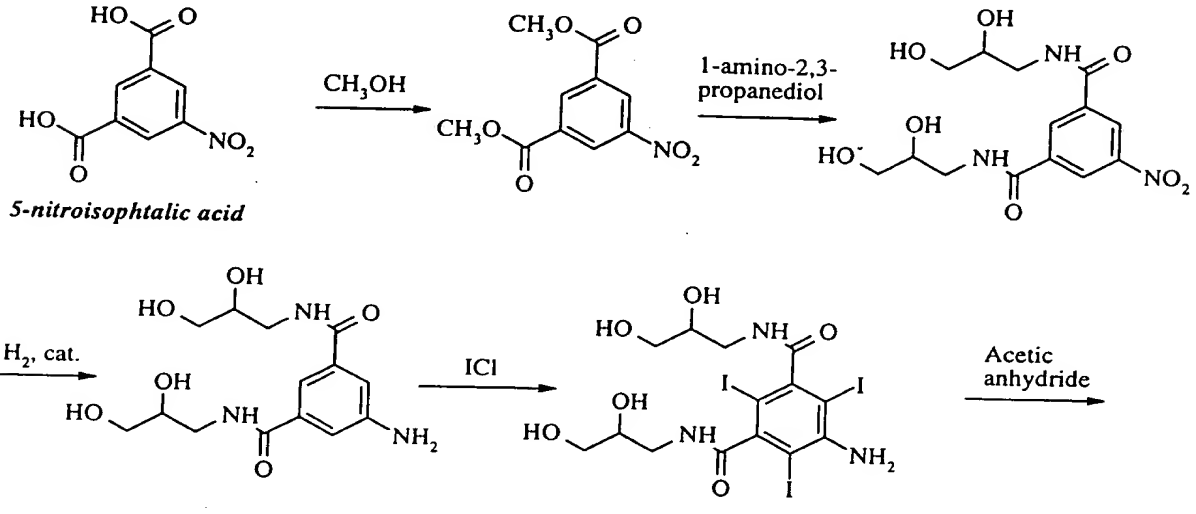
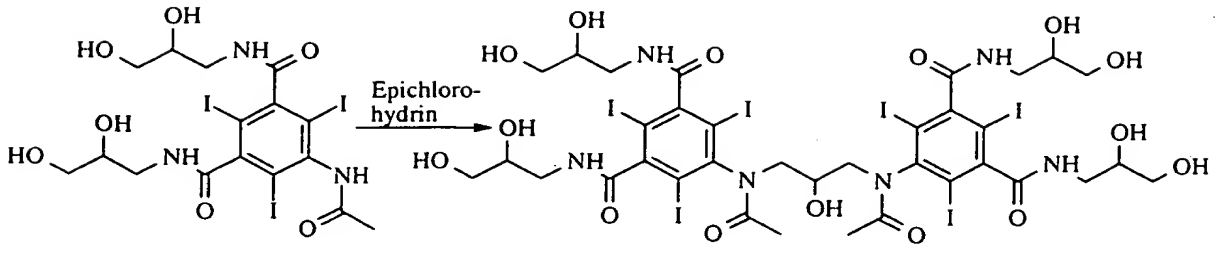
PROCESS

This invention is concerned with the synthesis of iodixanol.

Iodixanol (1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-2-hydroxypropane) is a non-ionic X-ray contrast agent which is currently manufactured in large quantities. A number of methods are known for its preparation but these are all multistep processes and the cost of the final formulated product thus mainly depends on these processes. It is therefore important to optimise these processes for both economic and environmental reasons.

Three main processes are known for the preparation of iodixanol, all of which start with 5-nitroisophthalic acid. In the first process (NO 161358), the following route is used, via the final intermediate 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide ("Compound A"):





Compound A *Iodixanol*

The problem with this process is that a yield of only 18% is reported in the given example, and the product is purified by preparative chromatography. When we have repeated the example, we have found that the low yield is due to incomplete conversion of Compound A to iodixanol. After 40-60% of the starting material is consumed, over-alkylation of iodixanol starts to dominate over the desired reaction, causing the net content of iodixanol in the reaction mixture to decrease. In fact, 40-60% conversion to iodixanol seems to be the maximum obtainable. Due to this low conversion, common crystallisation techniques are not able to purify the product to the necessary level, and preparative liquid chromatography is the only way to obtain a pure product. The combination of low yields with an expensive purification method such as preparative chromatography is a serious disadvantage in an industrial process.

Priebe *et.al.* (*Acta Radiol.* **36** (1995), Suppl. 399, 21-31) describe another route which avoids the difficult last step of the above process. However, the route involves eight reaction steps from 5-nitroisophthalic acid, which is undesirable, and one of the steps includes chlorination with thionyl chloride, which is extremely corrosive. Also, the introduction of the iodine atoms takes place very early in the sequence, which is disadvantageous as iodine is the most expensive

reagent in the process. The yield and final purification method for this route have not been reported.

The third route to iodixanol involves the synthesis of 5-amino-2,4,6-triiodoisophthalic acid (WO 96/37458) and then its dichloride (WO 96/37459), followed by conversion into Compound A (US 5705692) and finally dimerisation as in the first process above. This method thus has the same disadvantages as the first, and also uses an undesirable acid chlorination step.

We have now surprisingly found that unreacted Compound A from one dimerisation batch, as produced for example in the first and third processes described above, can be recovered from the reaction mixture by a very simple process, and reused in a later batch. This increases the net yield from successive batches on an industrial scale dramatically. Additionally, the removal of most of the unreacted Compound A from the reaction mixture allows the expensive preparative liquid chromatography purification to be replaced by conventional crystallisation methods, still providing iodixanol suitable for pharmaceutical use.

The invention thus provides a process for the preparation of iodixanol by dimerisation of Compound A in which, after the dimerisation step, unreacted Compound A is precipitated from the reaction mixture and recovered for re-use.

The dimerisation step itself may be carried out as described in NO 161368 and WO 98/23296, for example using epichlorohydrin, 1,3-dichloro-2-hydroxypropane or 1,3-dibromo-2-hydroxypropane as the dimerisation agent. The reaction is usually carried out in a non-aqueous solvent, preferably 2-methoxyethanol or methanol, and

generally results in the conversion of 40-60% of Compound A to iodixanol. Dimerisation in pure water or mixtures of water and one or more alcohols (e.g. C_{1-6}-alkanols) is also possible.

Precipitation of Compound A from a non-aqueous reaction mixture can be effected after addition of water, for example in an amount of 1-2, preferably 1.3-1.8 L/kg Compound A used as starting material. If water is present in the reaction mixture, the amount of water added for precipitation can be reduced accordingly. An alcoholic co-solvent (e.g. a C_{1-6} alkanol such as methanol) may additionally be used, for example in an amount of 0.5-2, preferably 0.8-1.5 L/kg Compound A used as starting material. In some instances, traces of undissolved material remain after the addition of water and alcohol and these can be dissolved by addition of alkali, e.g. sodium hydroxide. The pH of the solution is then adjusted to about 10-11 by addition of an acid, e.g. hydrochloric acid, to provoke precipitation of unreacted Compound A and if necessary the temperature can be adjusted to 15-40°C, preferably 18-30°C. The solution is optionally seeded with crystals of Compound A to initiate the precipitation of Compound A, while the iodixanol formed stays in solution.

Further addition of acid to a pH of 2-5, preferably 3-4, can increase the yield of the recovery process by increasing the supersaturation of non-ionic Compound A. After this final pH adjustment, the suspension is advantageously stirred for some hours to enhance the precipitation of Compound A, e.g. 4-30 hours, preferably 8-20 hours. The precipitate should then be separated from the reaction mixture by a conventional technique, such as centrifugation or filtration, and optionally washed with a suitable solvent, e.g. water or methanol.

The filtrate from the separation mainly contains iodixanol and small fractions of related iodinated aromatic compounds, in addition to salts and remaining epichlorohydrin and derivatives thereof. This mixture can be purified by conventional desalination and crystallisation methods to obtain iodixanol suitable for pharmaceutical use. Chromatographic purification of the crude iodixanol in the filtrate is not necessary.

The separated Compound A from the recovery process can optionally be recrystallised, for example from water/methanol or another alkanol. Thus, the moist material from the filtration/centrifugation may be dissolved in water in the presence of alkali. The amount of water should be about 2-7 l/kg of Compound A, preferably 3-5 l/kg. Alkali, e.g. aqueous sodium hydroxide, should be added until all traces of undissolved material are removed. The solution may optionally be filtered to remove remaining traces of undissolved matter. An alcohol, e.g. methanol (0.5-1.5 l/kg of Compound A, preferably 0.5-1.0 litres/kg) may then be added, and the mixture heated to 40-80°C, preferably 50-60°C. Adjustment of pH by an acid, e.g. hydrochloric acid, causes pure Compound A to precipitate. The mixture may optionally be seeded with a small amount of Compound A crystals. Maximum yield from the recrystallisation is obtained if the pH is finally adjusted to about 5-7, e.g. with hydrochloric acid, followed by cooling to 10-25°C. The slurry may optionally be stirred at this temperature to enhance the crystallisation, e.g. 2-18 hours. The precipitate is separated from the suspension by any conventional technique, for instance centrifugation or filtration, and optionally washed with water, methanol or another suitable alkanol. The recovered Compound A may advantageously be dried, e.g. under reduced pressure, before reuse in a new dimerisation.

Recovered and fresh Compound A may in any ratio be mixed and used in a new dimerisation reaction as described above, including subsequent recovery of unreacted substrate.

The following examples illustrate the invention.

EXAMPLE 1

Compound A (366 g) was dissolved in a solution of NaOH(23 g) in 2-methoxyethanol (360 ml) at 50°C. The temperature was decreased to 15°C when all solids were dissolved, and conc. HCl (28 g) was added to the solution. Epichlorohydrin (13 g) was added in one portion, and the reaction was monitored by HPLC. After 46 hours the content of iodixanol in the reaction mixture was 49.6%. Water (575 ml) was added, and the temperature was increased to 19°C. The solution was at this time clear, so no further addition of sodium hydroxide was necessary. The pH was adjusted to 10.8 by 18% hydrochloric acid, and the solution seeded with 1 g of Compound A. The pH of the resulting suspension was further pH-adjusted with 18% hydrochloric acid to pH 4.0. The suspension was left with stirring overnight before filtration and washing with water (60 ml) on the filter. The filtrate was further desalinated and crystallised by conventional methods, providing iodixanol suitable for pharmaceutical use. The material on the filter was analysed on HPLC, showing 94.3% Compound A and 5.1% iodixanol.

EXAMPLE 2

The recovered Compound A from Example 1 was taken directly from the filter without drying, and completely dissolved in water (440 ml) and 50% NaOH(aq) (15 ml). The solution was filtered through a 3 μm filter to

remove traces of insoluble matter, and some more water (50 ml) was added to the filtrate. Methanol (95 ml) was added to the solution, and the temperature was increased to 60°C. The pH was reduced from 11.5 to 9.8 with 18% hydrochloric acid, and 0.8 g seeds of Compound A was added. After 30 minutes, the pH was further reduced to 6 with 18% hydrochloric acid. The temperature was gradually reduced to 15°C, and the precipitated material was filtered, washed with methanol (140 ml) and dried under vacuum at 60°C. The yield of pure Compound A (> 99% by HPLC) was 118 g, corresponding to 32% of the starting material in Example 1.

The recovered Compound A (118 g) was combined with fresh Compound A (248 g) in a new dimerisation similar to Example 1, giving nearly identical results as in Example 1.

Claims

1. A process for the preparation of iodixanol by dimerisation of 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide ("Compound A") in which, after the dimerisation step, unreacted Compound A is precipitated from the reaction mixture and recovered for re-use.

2. A process according to claim 1 in which the dimerisation step is carried out using epichlorohydrin, 1,3-dichloro-2-hydroxypropane or 1,3-dibromo-2-hydroxypropane as the dimerisation agent in a non-aqueous solvent or in water or a mixture of water and one or more alcohols.

3. A process according to claim 2 in which the dimerisation agent is epichlorohydrin and the solvent is 2-methoxyethanol or methanol.

4. A process according to any preceding claim in which precipitation of Compound A is effected with water, optionally together with an alcoholic co-solvent.

5. A process according to claim 4 in which the pH of the mixture is adjusted to 10-11 with acid to provoke precipitation, the temperature adjusted if necessary to 15-40°C and the solution optionally seeded with crystals of Compound A.

6. A process according to claim 5 in which further acid is added to a pH of 2-5.

7. A process according to any preceding claim in which the Compound A recovered is recrystallised.

8. A process according to claim 1 in which, after separation of Compound A, the iodixanol-containing mixture is purified without the use of chromatographic methods.

ABSTRACT

PROCESS

A process for the preparation of iodixanol by dimerisation of 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-isophthalamide ("Compound A") in which, after the dimerisation step, unreacted Compound A is precipitated from the reaction mixture and recovered for re-use. The process substantially increases the net yield of iodixanol and simplifies its purification.